REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-5, 7-9, 11-17 and 19-37 are in this case. Claims 38-50 have been withdrawn from further consideration, as being drawn to a non-elected invention. Claims 1-5, 7-9, 11-17 and 19-37 have been rejected. Claims 1, 7, 11, 12, 13, 19-21, 26, 29-31, 36 and 37 have now been amended.

Interview Summary

In the Interview held on with the Examiner on September 23, 2004, the rejections raised by the Examiner in the instant Official action were discussed. In particular the 35 U.S.C. § 112 second paragraph rejections relating to the terminology used in the claims and the 35 U.S.C. § 112 first paragraph rejections relating to the % homology and to the species of embryo *vs.* uterus were discussed.

It was agreed that the term implanting as used in the claims is identical to the term placing as placing is the sole and only man made action involved with implanting in the context of the claims.

The Examiner explained that his rejection of the language "purified recombinant heparanase having at least 95 % homology to SEQ ID NO:1" is due to the phrase "having at least 95 % homology to SEQ ID NO:1".

The Examiner's attention was directed to the fact that the Examiner has in the past allowed the language "at least 95 % homology" is a sister application Serial No. 09/988,113, now U.S. Patent No. 6,790,658, both the sister and the instant applications claim priority of U.S. Patent Application No. 08/922,170, filed September 2, 1997, now U.S. Patent No. 5,968,822, issued October 19, 1999, witch is also incorporated by reference in both. Applicant asserted in this regard that the instant application should receive similar consideration with respect to the language "at least 95 % homology".

Applicant agreed to limit the claims to implantations involving embryo and uterus of the same species.

35 U.S.C. § 112 Second Paragraph Rejections

The Examiner has rejected claims 1-5, 7-9, 11-17 and 19-37 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner's rejection is respectfully traversed. Claims 1, 7, 11, 12, 13, 19-21, 26, 29-31, 36 and 37 have now been amended.

In particular, the Examiner states that that the recitation of the two words "implantation" and implanting in the claims is confusing.

While disagreeing with the Examiner, Applicant has chosen the replace the verb "implanting" with the equivalent verb "placing" to thereby ensure that there is no confusion.

As the man made action associated with "implanting" is in effect "placing", "implanting" and "placing" in this context are synonyms. Indeed, these terms are interchangeably used in the art to identify the same man made action, i.e., placing an embryo in a receptive uterus.

Evidently, no new matter was added to the claims by this amendment, since placing is the sole and only man made action involved with implanting in the context of the claims.

In view of the above, Applicant believes to have overcome the Examiner's 35 U.S.C. § 112, second paragraph, rejection.

35 U.S.C. § 112 First Paragraph Rejections

The Examiner has rejected claims 1-5, 7-9, 11-17 and 19-37 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors, at the time that the application was filed, had possession of the claimed invention. The Examiner's rejections are respectfully traversed. Claims 1, 7, 11, 12, 13, 19-21, 26, 29-31, 36 and 37 have now been amended.

In particular, the Examiner asserts that the recitation "purified recombinant heparanase having at least 95 % homology to SEQ ID NO:1" is not supported by the original application.

Applicant wishes to address the Examiner's attention to the following.

1. In the interview the Examiner explained that this rejection is due to the use of wording "at least 95 % homology to SEQ ID NO:1," which, in the Examiner's opinion, finds no support in the specification as filed.

2. The related application data for the instant application, brought here as filed, is as follows:

> This is a continuation-in-part of U.S. Patent Application No. 09/260,037, filed March 2, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/140,888, filed August 27, 1998, which is a continuation-in-part of U.S. Patent Application No. 09/046,475, filed March 25, 1998, now, U.S. Patent No. 6,153,187, issued November 28, 2000, which is a continuation-in-part of U.S. Pat. application No. 08/922,170, filed September 2, 1997, now U.S. Patent No. 5,968,822, issued October 19, 1999. This application further claims the benefit of priority from U.S. Provisional Patent Application No. 60/240,037, filed October 17, 2000. The specifications of the above cited applications are incorporated herein by reference. (Emphasis added)

3. The related applications data of the instant application was incorporated therein by reference.

4. U.S. Patent No. 6,790,658 (Serial No. 09/988,113) was issued by the Examiner currently examining the instant application with the following claim language:

> 1. An isolated polynucleotide fragment comprising a polynucleotide sequence encoding a polypeptide having heparanase catalytic activity, wherein said polypeptide shares at least 95% homology with SEQ ID NO:10 as determined using default parameters of a DNA sequence analysis software package developed by the Genetic Computer Group (GCG) at the University of Wisconsin. (Emphasis added).

Note the use of the language "at least 95 % homology to SEQ ID NO:10" in the claim language.

Also note that SEQ ID NO:10 in U.S. Patent No. 6,790,658 (Serial No. 09/988,113) and SEQ ID NO:1 of the instant application describe identical polypeptides, both are of human heparanase.

5. The related applications data for U.S. Patent No. 6,790,658 (Serial No. 09/988,113), as appears in the issued patent reads as follows:

> This is a continuation of U.S. patent application Ser. No. 09/776,874, filed Feb. 6, 2001, which is a continuation of U.S. patent application Ser. No. 09/258,892, filed Mar. 1, 1999, now abandoned which is a continuation-in-part of PCT/US98/17954, filed Aug. 31, 1998, which is a continuation-in-part and claims priority from U.S. patent application Ser. No. 09/109,386, filed Jul. 2, 1998, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/922,170, filed Sep. 2, 1997, now, U.S. Pat. No. 5,968,822. (Emphasis added).

6. Hence, claim 1 of U.S. Patent No. 6,790,658 (Serial No. 09/988,113) derives its priority of U.S. Patent Application Serial No. 08/922,170 (filed September 2, 1997, now, U.S. Patent No. 5,968,822), whereas the text of the very same application (Serial No. 08/922,170) is incorporated by reference into the specification of the instant application (see section 2 of this argument above), and which also claims priority thereof.

7. In a response to an Official action issued for U.S. Patent No. 6,790,658 (Serial No. 09/988,113) on January 5, 2004 by Examiner Hutson, it was argued in this regard as follows:

> The Examiner has rejected claims 1, 3, 8, 10, 11, 13, 18, 19, 20, 22, 27, 28, 29 30 and 31 under 35 USC 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the relevant art to make and use the invention commensurate in scope with these claims. The

rejections of the Examiner are respectfully traversed.

Specifically, the Examiner states that the specification, while being enabling for a polynucleotide fragment comprising a polynucleotide sequence encoding a polypeptide of amino acid sequence SEQ ID NO:10, does not reasonably provide enablement for any polynucleotide fragment comprising a polynucleotide sequence encoding a polypeptide which shares 70% homology with SEQ ID NO:10, such that one of ordinary skill in the art would be forced to perform undue experimentation in order to fulfill the invention as claimed.

While continuing to traverse the Examiner's rejections, and in order to expedite the prosecution of this case, Applicant has chosen to amend claims 1, 10, 11, 20, 28, 29 and 31 to recite that the "polypeptide shares at least 95% homology with SEQ ID NO:10" instead of "at least 70 %" as previously.

Nevertheless, Applicant wishes to repeat some of Applicant's arguments previously submitted, as follows:

Page 56, lines 3-18 clearly describe use of the amino acid sequence of human heparanase to search for homologous sequences in DNA and protein databases, enabling identification of candidate amino acids that participate in the heparanase active site. Lines 11-13 refer to 81% homology between deduced amino acid sequences from mouse and human *hpa* genes. Homology searches using computer servers and various databases are described on page 83, bridging page 84, lines 1-2.

Page 37, lines 12-22 describes a preparation comprising a recombinant protein, in which the protein includes a polypeptide encoded by a polynucleotide capable of inducing heparanase activity after transfection into a cell, in which the cell is characterized by lacking such heparanase activity before transfection. Applicant feels that this recitation includes a clear structure-function relationship, given the recitation of the polynucleotide that is capable of inducing heparanase activity.

The Examiner contends that one of ordinary skill in the art would not know which changes in the polypeptide sequence could be made while preserving heparanase function. Applicant notes that the present Application clearly teaches an assay for heparanase activity, as described on p. 74, line 8 to the end, bridging to p.75, lines 1-3. Such an assay could easily be used by one of ordinary skill in the art to determine which proteins having a sequence that falls within the definition of at least 70% homology in the claim also have heparanase activity. A

definition of "heparanase activity" is also provided on p. 57, lines 15-20.

The specification at page 72, lines 4 to end, spanning page 73, lines 1-6 describes purification and characterization of heparanase with a purification procedure initiated with Heparin-Sepharose chromatography, followed by gel filtration and pooling of active column fractions, wherein a quantity of the protein after the purification correlates with heparanase activity in the pooled active column fractions. Applicant feels that this recitation overcomes the rejections of the Examiner in that the structural limitations of size and also behavior with Heparin-Sepharose chromatography and gel filtration are all included. Determination as to whether a protein falls within the boundaries of the claims may be achieved by this simple assay, such that undue experimentation is not required.

Applicant notes that the revised Guidelines state in footnote 42 that "examples of identifying characteristics include sequence, structure, binding affinity, binding specificity, molecular weight and length.... For example, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities or antibody cross-reactivity". Applicant feels that these recited limitations clearly fall within these categories of permissible identifying characteristics, which clearly distinguish the protein of Applicant and which clearly provide structure-function relationships.

Applicant further notes that the definition of "one of ordinary skill in the art" has been held in numerous court cases to depend upon the art in question; in fields such as that of the present invention, clearly the art would indicate that "one of ordinary skill in the art" could actually be a team of Ph.D. level scientists. Such a team could easily perform the above-described assay in the present Application without undue experimentation, in order to determine whether a particular sequence encodes for a heparanase polypeptide.

For purposes of further clarification, Applicant has submitted alignment data in the Affidavit previously filed in this case, showing the homology (and differences) between human, rat, mouse and chicken heparanase sequences. Some important shared features such as the heparan sulfate binding site are marked. This information further supports Applicant's statements with regard to the ability of one of ordinary skill in the art to

readily recognize a heparanase protein as such.

Furthermore, Applicant notes that such homology can even be detected in a heparanase protein that has sequence homology of less than 70%; while for the present invention claims now recite "at least 95%" homology.

Applicant furthermore notes that the claims do not require *prediction of protein structure from a sequence*, which seems to be the goal of the reference cited by the Examiner, Ngo et al. The claims are sufficiently supported by the demonstration that variation in sequence homology is possible, to the degree recited by the claims; and that a functional, easily performed assay is taught, which enables one of ordinary skill in the art to determine whether a protein is indeed a heparanase. Certainly, locating homologous proteins according to a known sequence is a relatively easy task. After all, the Human Genome Project has used such sequence comparisons to determine the function of a protein having a new sequence, once the sequence of at least one member of that protein's family was known [Benner et al. Res Microbiol. 2000 Mar;151(2):97-106; Bork & Koonin Nat Genet. 1998 Apr;18(4):313-8]. Such a comparison is a known tool for the average researcher, and was also available to one of ordinary skill in the art at the time of filing of the priority application. The further provision of an assay enables "false positives" to be easily detected.

Thus, Applicant notes that the criteria stated by the Examiner as being raised by *In re Wands* are all answered in this Response and in the present Application, thereby giving positive support to the present claims. In particular:

1) The quantity of experimentation necessary is minimal, and could certainly be performed by one of ordinary skill in the art, particularly given that such an individual could be a team of scientists. It should be noted that many other cases indicate that merely tedious or laborious experimentation is not considered to be "undue", even if a large amount of experimentation is required (see for example *Ex parte* Erlich 3 U.S.P.Q.2d (B.P.A.I. 1982); and *Ex parte* Jackson, 217 U.S.P.Q. (B.P.A.I. 1982), which indicated that quantity of experiments alone is not sufficient to be "undue", as long as the experiments were routine). Indeed, enablement was upheld for patents which required trial and error experimentation (see for example Durel Corp. v. Osram Sylvania Inc., 52 U.S.P.Q.2d (D.Ariz. 1998)).

2) Sufficient guidance is presented to easily determine whether a particular polypeptide is in fact a heparanase, particularly given the described heparanase assay in the present Application, which is sufficiently simple to be easily performed by one of ordinary skill in the art; guidance is also provided to determine the degree of homology which is also explicitly stated in the claims.

3) Working examples are provided of heparanases having different degrees of homology, as well of how to determine such homology.

4) The nature of the invention is quite well known, as heparanases themselves were known, although their sequences were not; it is not correct to present arguments and references which suggest that the claims relate to a generalized, non-specific protein, when in fact they relate to a specific, well-defined and well-characterized family of proteins, which is the heparanase family.

5) The state of the prior art *at the time of filing of the parent of the present Application* clearly indicated that broad homology to a particular sequence could be determined in a well-characterized manner, as for a family of proteins having a defined function, which is the case for heparanase [Koch-Nolte et al. Genomics. 1997 Feb 1;39(3):370-6; Koonin et al. Proc Natl Acad Sci U S A. 1995 Dec 5;92(25):11921-5].

6) The relative skill of those in the art was already quite high at the relevant time, particularly for a team of skilled scientists, and particularly for comparing sequences of a family to determine homology [Seldin MF, Methods. 1997 Dec;13(4):445-57].

7) As noted above, heparanase proteins belong to a well-characterized family, which has predictable behavior and sequence homologies.

8) The claims are not any broader than the working examples, and are certainly not as broad as the known homology of those sequences that are described in the present Application and the affidavit previously filed.

8. Based on the above and the fact that the Examiner acknowledged that there is support for "at least 95 % homology ..." in the specification of U.S. Patent No. 6,790,658 (Serial No. 09/988,113), which support arrives from the original application first disclosing the human heparanase gene and protein sequence, i.e., U.S. Patent Application No. 08/922,170 (filed September 2, 1997, now,

U.S. Patent No. 5,968,822), from which priority is claimed by the instant application and which specification is incorporated by reference into the instant application, it is argued that support for the language 95 % homology is clearly present in the specification of the instant application as the instant application should be examined under similar criteria as applied by the same Examiner in the examination of U.S. Patent No. 6,790,658 (Serial No. 09/988,113), in which the issue of support for the language "at least 95 % homology ..." was addressed at length and the Examiner's rejections in this regard were overcame.

In view of the above, Applicant believes to have overcome the Examiner's 35 U.S.C. § 112, first paragraph, rejections.

35 U.S.C. § 112 First Paragraph Rejections

The Examiner has further rejected claims 1-5, 7-9, 11-17 and 19-37 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors, at the time that the application was filed, had possession of the claimed invention. The Examiner's rejections are respectfully traversed. Claims 1, 7, 11, 12, 13, 19-21, 26, 29-31, 36 and 37 have now been amended.

In particular the examiner states that there is no enablement in the specification for transplantation of an embryo from one species to a receptive uterus of another species.

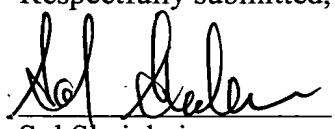
Applicant has chosen to amend the claims to clearly state that the embryo and the uterus are of the same species, to thereby overcome the Examiner's rejections.

Ample support is found for this amendment in the specification. For example, all of the experimental data disclosed in the specification of the instant application relates to embryo transplantation whereby the embryo and uterus are of the same species.

In view of the above, Applicant believes to have overcome the Examiner's 35 U.S.C. § 112, first paragraph, rejection.

In view of the above amendments and remarks it is respectfully submitted that now amended independent claims 1-5, 7-9, 11-17 and 19-37 are now in condition for allowance. Prompt Notice of Allowance is respectfully and earnestly solicited.

Respectfully submitted,



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